You can't tell a rickettsiosis from its spots: the expanding spectrum of spotted fever in the United States

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The findings and conclusions are those of the presenter and do not necessarily reflect the views of US Department of Health and Human Services or the Centers for Disease Control and Prevention

Rocky Mountain spotted fever: the disease

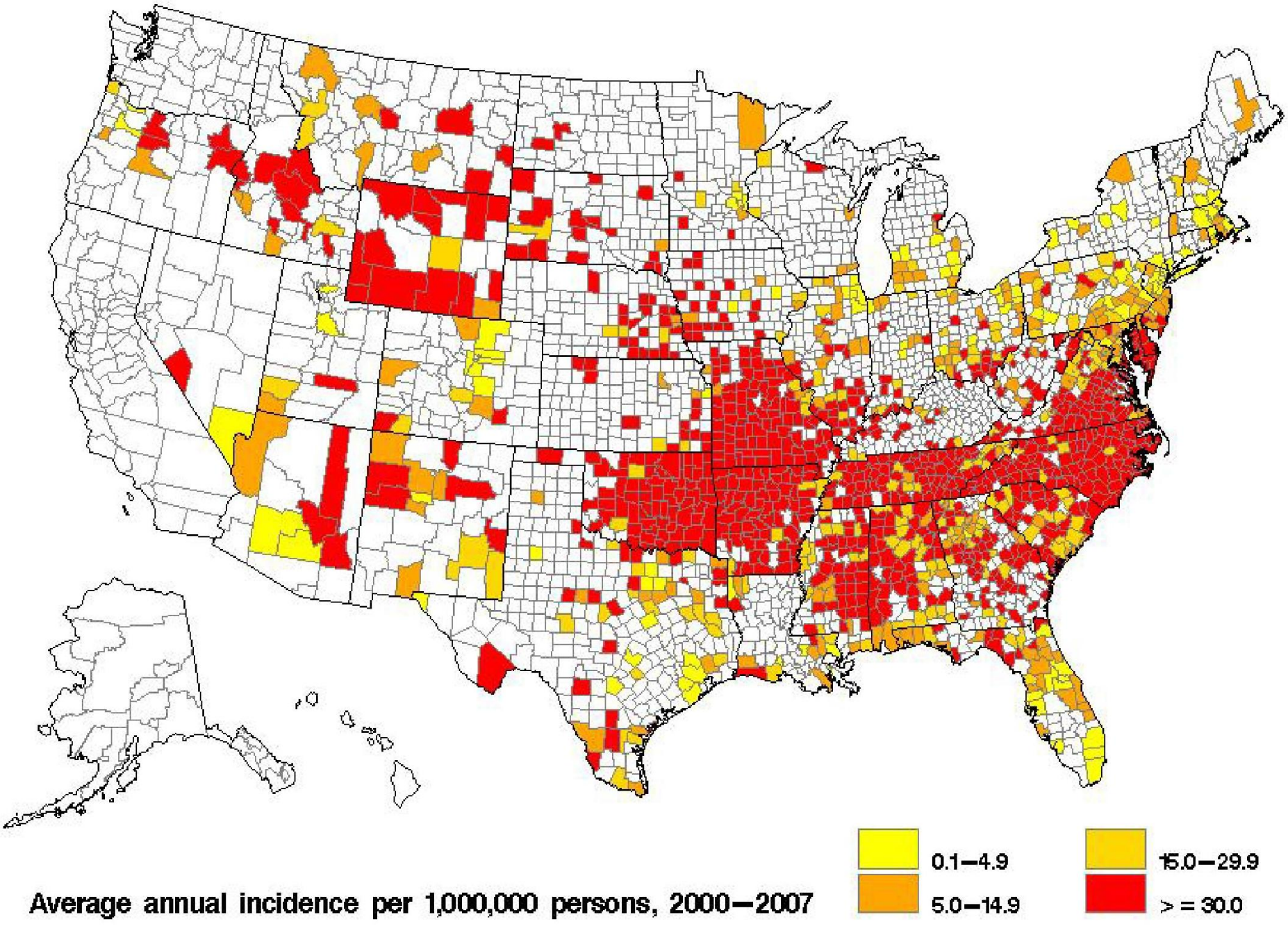
- *Rickettsia rickettsii* can infect vascular endothelial cells of every organ in the body
- Disease may involve lungs, heart, kidneys, gastrointestinal tract, central nervous system and skin
- High fever, headache, nausea, vomiting
- Macular rash starts ~3 days evolves into petechiae ~6 days, involves palms and soles
- Most deaths occurs within 9 days

RMSF: historical case-fatality rates

Location	Interval	Case fatality rate (N)
Bitterroot Valley, MT	1904-1923	63% (238)
Long Island, NY	1926-1934	30% (10)
Cape Code, MA	1955-1968	15% (13)
Mississippi	1969-1972	18% (49)
North Carolina	1966-1995	14% (114)
White Mountain, AZ	2002-2004	12% (16)

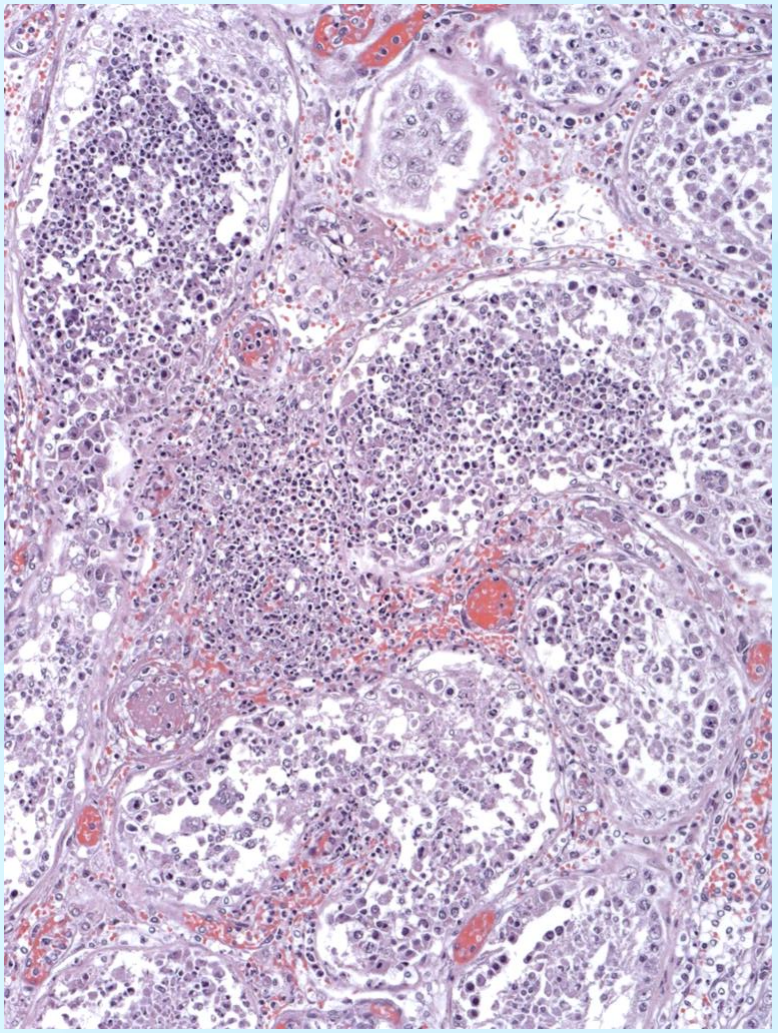
Doxycycline is *the* recommended drug

- Adults: 100 mg twice daily for 5-10 days
- Children <45 kg: 2.2 mg/kg body weight per dose, twice daily
- Therapy most effective within the first 5 days of illness
- Chloramphenicol the only other alternate drug
- Penicillins, cephalosporins, aminoglycosides, and macrolides are ineffective

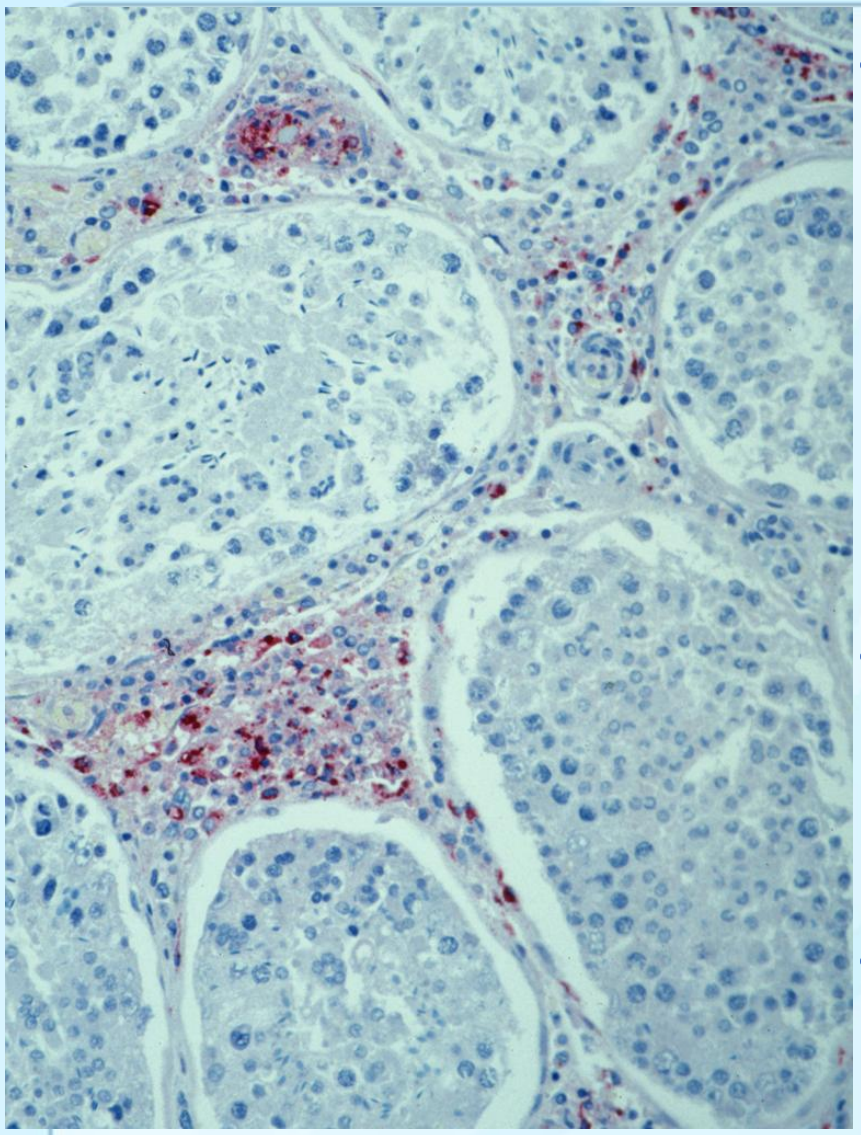

0.1–4.9
5.0–14.9
15.0–29.9
> = 30.0
Average annual incidence per 1,000,000 persons, 2000–2007

New York State, 1998

- 9-year-old Labrador retriever first seen at a veterinary clinic for rapidly progressive lethargy
- Condition worsened over next several days, developed fever, stupor, and scrotal swelling and erythema
- Dog euthanized and necropsy performed



Testis showing lymphocytic vasculitis



Testis, immunohistochemical stain for *R. rickettsii* (red)

- Dog's owner had been hospitalized the day after the death of her dog with high fever, nausea, vomiting, and thrombocytopenia
- Gradually recovered, but diagnosis unknown
- Physician contacted; patient subsequently found to have a seroconversion to *R. rickettsii*

ROCKY MOUNTAIN SPOTTED FEVER

A STUDY OF COMPLEMENT FIXATION IN THE SERUM OF CERTAIN DOGS

CHARLES C. SHEPARD AND NORMAN H. TOPPING

From the Division of Infectious Diseases, National Institute of Health, Bethesda, Maryland

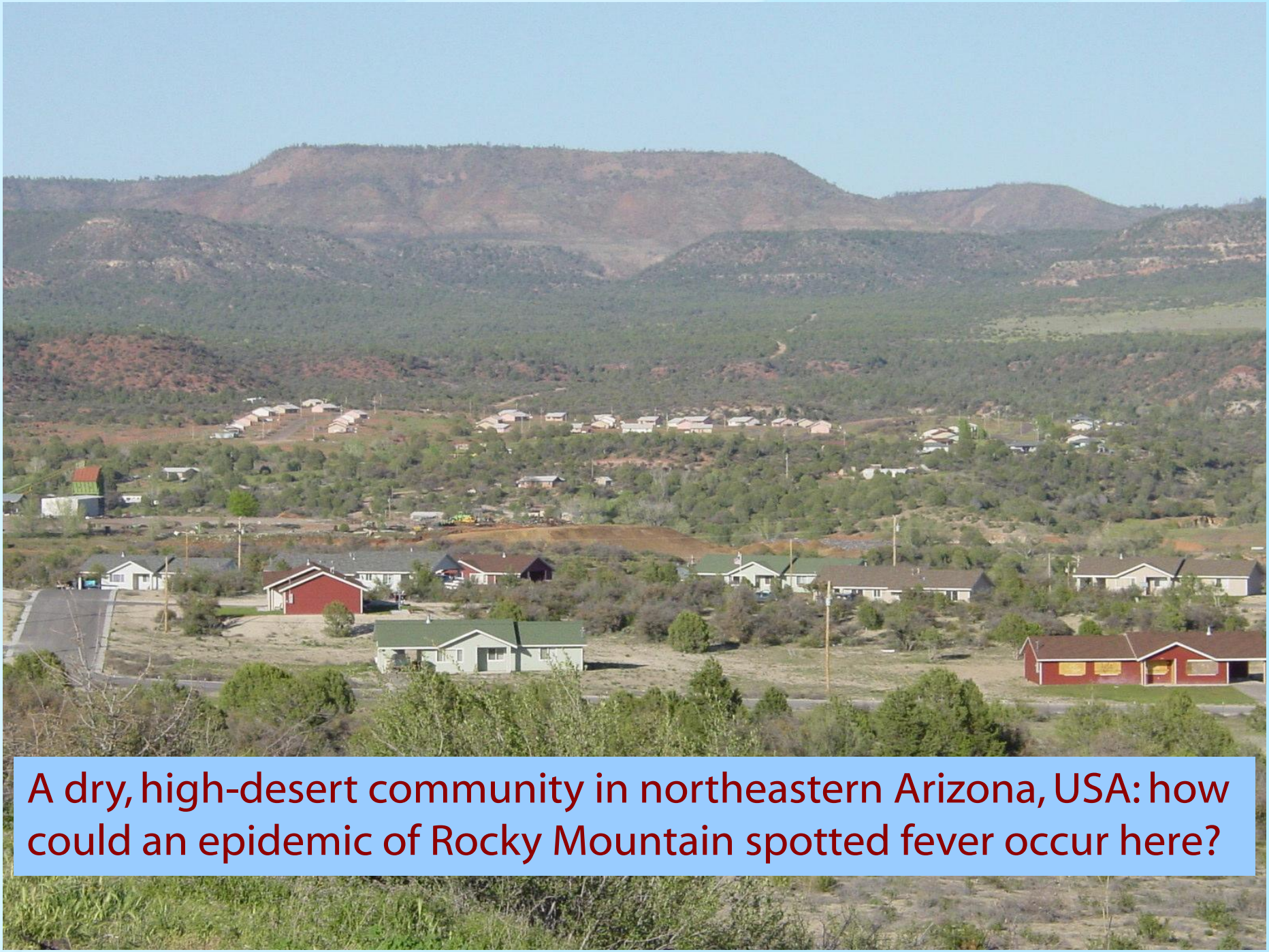
During the summer of 1943 several members of the New York State Department of Health called our attention to a possible connection between a case of Rocky Mountain spotted fever and a previous illness in the patient's dog. The sequence of events was briefly as follows: On the first of May, the B's took their 4-year-old male Doberman pinscher dog from New York City to East Hampton, Long Island. On May 14, the dog became ill with fever and the tory gave the following results:*

Agglutination:	
Specimen 6/23	
Proetux OX-19:	Positive 1:640
Specimen 6/28	
Proteus OX-19:	Positive 1:640
Complement Fixation	
Specimen 6/23	
Rocky Mountain spotted fever antigen:	Positive 1:2048
Specimen 6/28	
Rocky Mountain spotted fever antigen:	Positive 1:2048

J Infect Dis 1946;78: 63-68

Arizona, 2003

- Young boy dies in a small community in a mountainous region of eastern Arizona with fever and petechial rash
- CDC confirms the cause of death as Rocky Mountain spotted fever
- 14 more cases diagnosed from the same community during 2004
- No *Dermacentor* ticks reported in this region
- Investigations initiated by CDC to determine the cause



A dry, high-desert community in northeastern Arizona, USA: how could an epidemic of Rocky Mountain spotted fever occur here?

Free-roaming dogs were everywhere…

This is high desert and is very hot during the day. The dogs often went under the houses for shade. Children often played under the houses.

Surprisingly, we found thousands of ticks in the concrete and dirt under each of the houses, and not the tick we expected…

The brown dog tick: an unexpected vector of Rocky Mountain spotted fever in Arizona

Rhipicephalus sanguineus

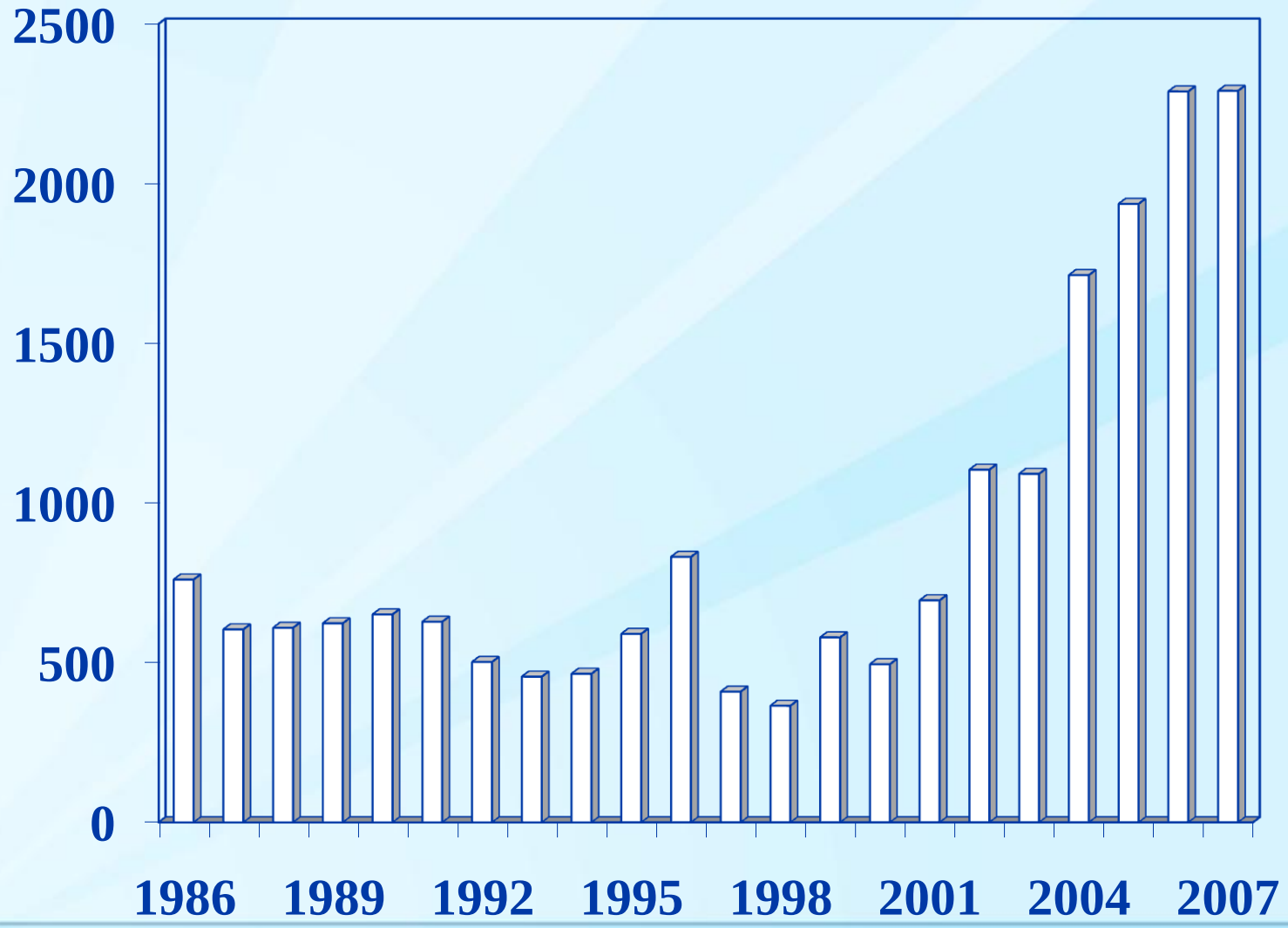
- Sole vector of ongoing epidemic in eastern Arizona
- Strongly associated with dogs and peridomestic habitats—very resistant to desiccation
- Very common tick in the US; seldomly bites humans
- Contribution to epidemiology of RMSF may be greater in than appreciated

- Analysis of 329 archival canine serums samples from same community collected in 1996: only 2 (0.6%) with relevant titers to *R. rickettsii.*

- 2003 canine serosurvey: robust anti-*R. rickettsii* antibodies in 70 (72%) of 97 dogs

- High titers also detected in 57% of dogs from another community 60 miles away; outbreak of RMSF occurred the following year

Reported cases of RMSF, United States, 1986-2007



Rickettsia rickettsii in *Dermacentor variabilis**
An epidemiologic-ecologic disconnect?

Location, year	No. (% infected)
MD, 1951-53	17,649 (0.25)
NC, 1982	2,123 (0.05)
OH, 1984-89	12,631 (0.06)
MD, 2002	392 (0)
TN, 2007-08	555 (0)
DE, MD, NJ, 97-09	1,400 (0.07)

*Price, 1954; Gordon et al., 1984; Burgdorfer, 1988; Pretzman et al., 1990; Ammerman et al., 2004; Moncoyo et al., 2010; Stromdahl et al., in press.

Tick-borne spotted fever rickettsiae in the United States

Rickettsia rickettsii
Rickettsia parkeri
Rickettsia sp. 364D
Rickettsia rhipicephali
Rickettsia montanensis
Rickettsia peakockii
“Rickettsia cooleyi”
“Rickettsia amblyommii”
Rickettsia sp.“Tillamook”
Rickettsia sp.“parumapertus”

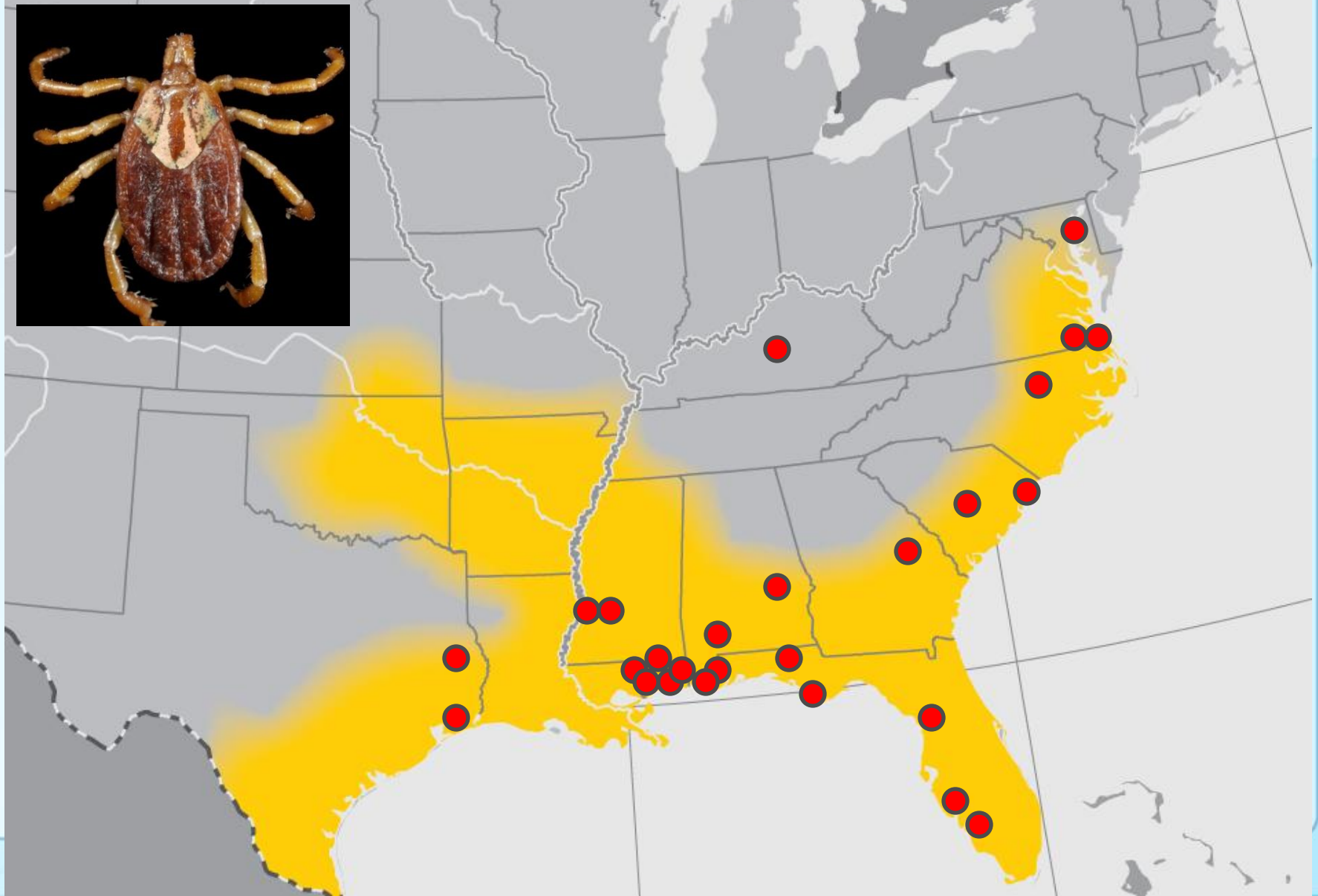
- In 1937, R. R. Parker initiates a survey of ticks in Liberty County, Texas, following an outbreak of illnesses diagnosed as "RMSF"

- Guinea pigs inoculated with *Amblyomma maculatum* ticks develop febrile illness, similar to, but milder than classical RMSF

"An unnamed, apparently new rickettsia has been repeatedly isolated at the Rocky Mountain Laboratory during the past nine years from specimens of *Amblyomma maculatum*, a tick of wide distribution in the Southern States…the presumptive evidence from animal experimentation suggests that human infection might be confusingly similar to spotted fever"

R.R. Parker, 1948

Confirmed and suspected cases of *Rickettsia parkeri* rickettsiosis through 2010



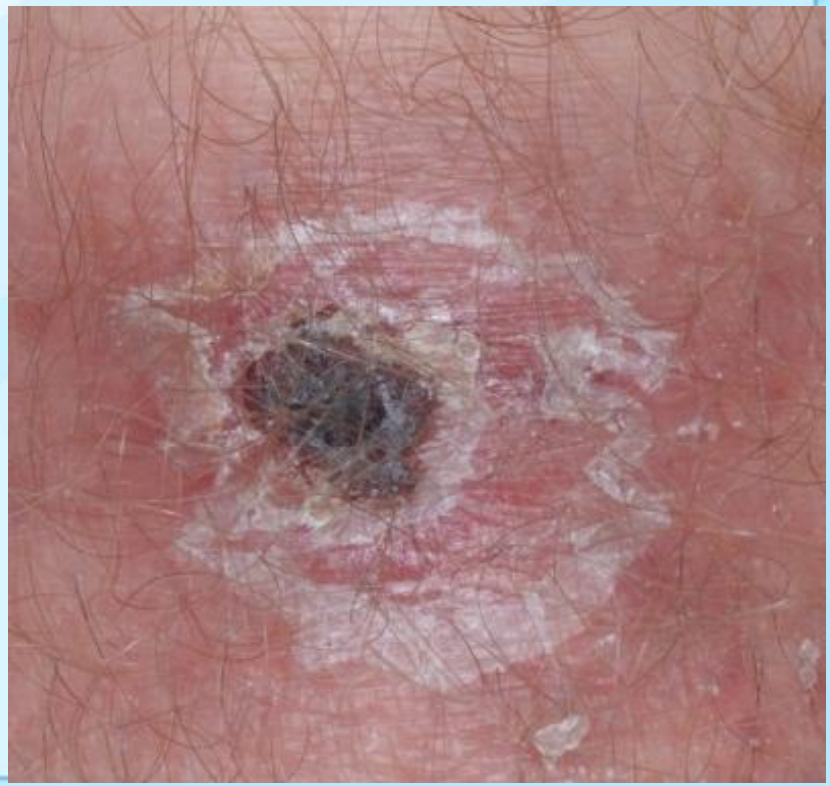
Rocky Mountain spotted fever

Rickettsia parkeri rickettsioisis

RMSF vs. *Rickettsia parkeri* rickettsiosis

Clinical feature	Rocky Mountain spotted fever (n = 208)	*R. parkeri* rickettsiosis (n = 15)*
Fever	100%	100%
Headache	72%	80%
Maculopapular rash	83%	87%
Petechial rash	47%	13%
Vesicular rash	0	40%
Eschar	0	93%
Hospitalization	78%	33%
Death	7%	0

*Clin Infect Dis 2008;47, Arch Dermatol 2010 ; 146



Eschars on patients with *R. parkeri* rickettsiosis

Vesicular rash of
R. parkeri rickettsiosis

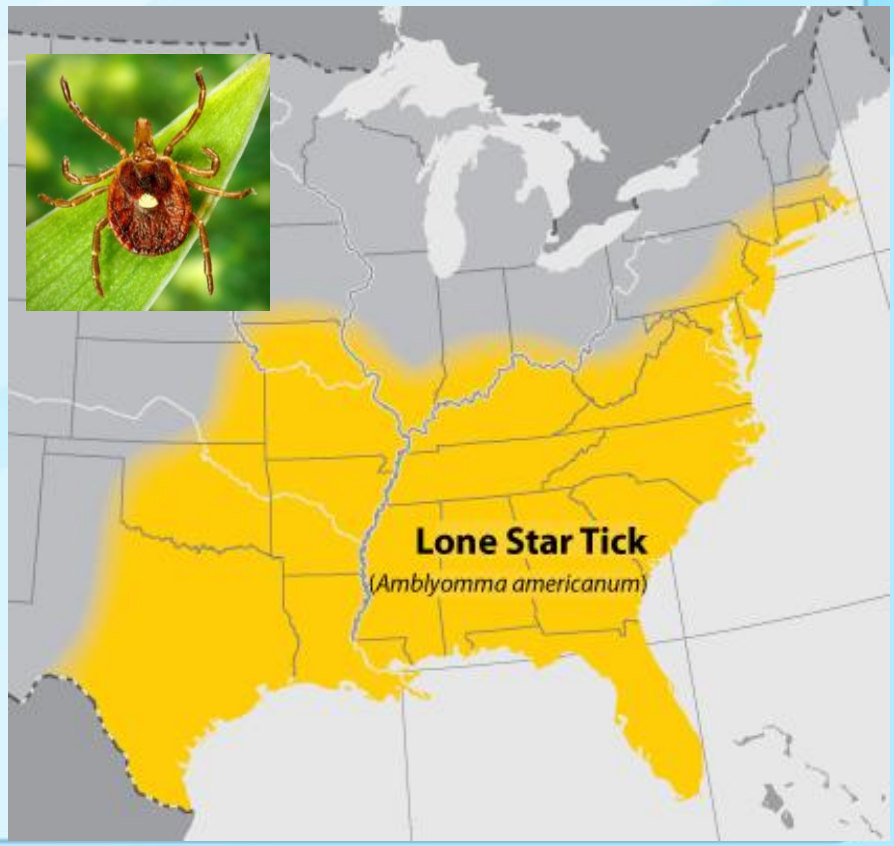
R. parkeri rickettsiosis: initial diagnoses and IFA titers

Pt.	Initial diagnosis	Initial IFA titer to *R. rickettsii* antigens
65/M	RMSF	1024
50/F	RMSF	512
83/M	RMSF	1024
40/M	rickettsialpox	1024
51/M	rickettsialpox	256
60/F	RMSF	64
53/F	rickettsialpox	32
78/F	RMSF	1024
23/M	spider bite	<32
53/M	*R. parkeri* infection	<32
72/M	RMSF	<32
30/M	cellulitis	64

Rickettsia parkeri: infection of *Amblyomma* ticks in the southeastern US

- *Amblyomma maculatum:* relatively high infection prevalence (~15% - 40%) in questing adult ticks from MS, FL, GA, and VA
  - 40 (28%) of144 from NC

- *Amblyomma americanum*: infections much less common, ~0.2% - 1% of ticks from GA, MS, KY, and TN



How many *Ehrlichia spp.* infections are misdiagnosed as "RMSF"?

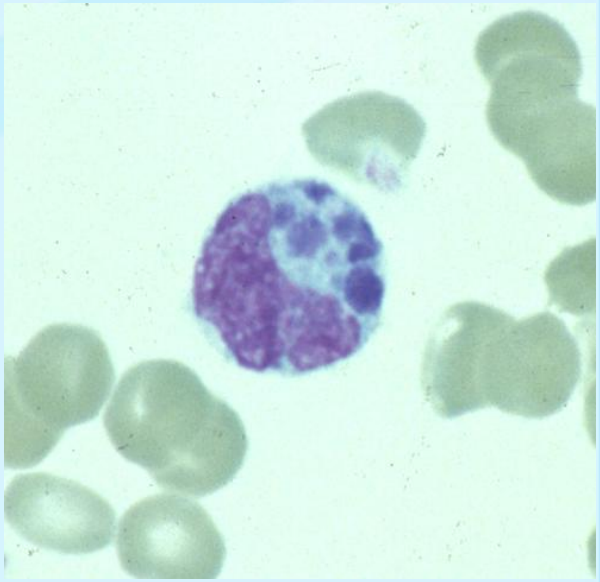
- *Amblyomma americanum:* the most common and widely distributed human-biting tick in the southeastern US; relatively high infection prevalence (~2% to 5%)

- Ehrlichiosis shares many clinical features with RMSF; rash present in ~30%

- Similar seasonal pattern, exposure history, and response to doxycycline

- Carpenter et al., 1999: 9 (56%) of 16 patients with fever and tick bite over 2 years

- Fishbein et al., 1987: 3 (10%) of seronegative 'RMSF' cases during 1985-86



"The American white-tailed deer… adjusts remarkably well to human activity, to cities, and to agriculture. It is a deer of ecological havoc, a survival virtuoso…"

Valerius Geist, 1998

What is the contribution of *Rickettsia amblyommii*?

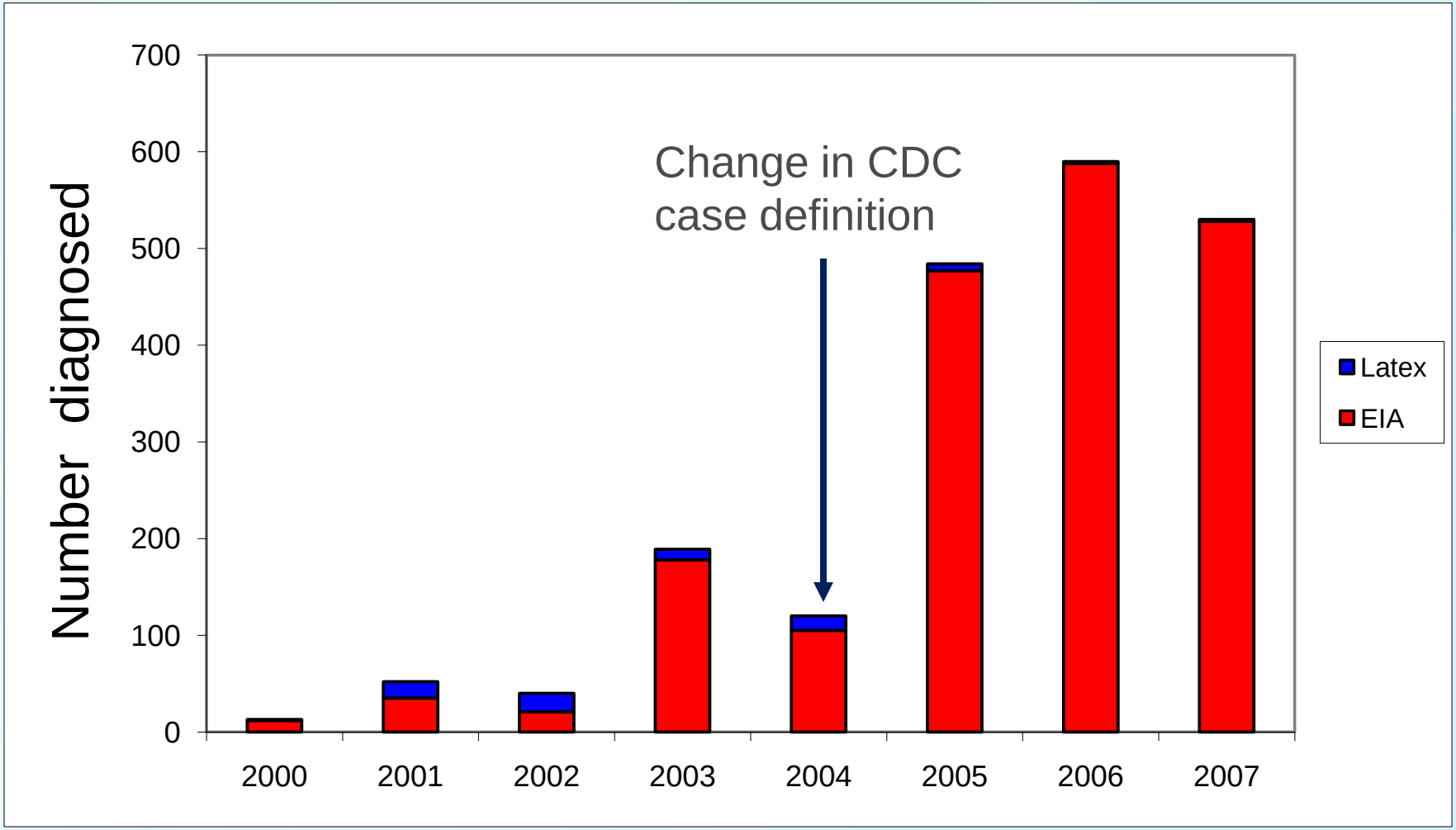
- Lone star ticks frequently infected with *Rickettsia amblyommii* (~40%-60%)
- *R. amblyommii* identified in salivary glands of lone star ticks
- Multiple longitudinal studies document asymptomatic seroconversion to spotted fever rickettsiae in as many as 33% of persons exposed to *A. americanum*-infested habitats
- Apperson et al., 2008: seroconversion of symptomatic patients to *R. amblyommii*, but not *R. rickettsii* antigens

Diagnostic assays: pitfalls and problems

- Serologic methods used to diagnose >99% of all cases of spotted fever
- Seroconversion using IFA is considered the reference standard, but not sufficient to specifically identify the causative *Rickettsia* species
- Diagnostic levels of antibodies to spotted fever group rickettsiae occur in ~5%-10% of general US population!
- Non-quantitative assays (EIA) used increasingly; cannot be used to document seroconversion

Changing diagnostic landscape

RMSF cases diagnosed by serologic methods other than IFA 2000-2007 (CRFs)



Closing comments

- Epidemiologic data for RMSF is likely confounded by other milder rickettsioses

  -change in surveillance definition in 2010 from "RMSF" to "spotted fever rickettsiosis"

- Accuracy in diagnosis imperative: molecular techniques are the key to separating similar, yet distinct, spotted fevers

  -skin biopsy

  -eschar swab

Acknowledgments

- Marcee Toliver and Barry Engber
  NC Department of Environmental and Natural Resources
- Andrea Varela-Stokes
  Mississippi State University

14-POUND TICK FROM WOMAN'S BACK!

Bug imbedded itself into her flesh in 1987 — and grew & Grew & GREW!

bathroom mirror," said the 60-year-old woman.

"I'm scared of bugs and just seeing it there made me shudder.

"I should have seen a doctor right then and there but I didn't want to think about it. I convinced myself that it would crawl away all by itself. I put it out of my mind altogether.

That was easy in the beginning when the tick was still small. When it got bigger, I had to work at it."

As the weeks turned into months the tick continued to feast on Miss Gillon's blood. By the end of the year it was as big as a dinner plate. And even though she began to wear loose clothes to keep it hidden, people still noticed the lump on her back and asked questions about it.

"It was so embarrassing that I became a recluse," she said. "I didn't leave the house for anything. I even had a delivery service bring groceries so I wouldn't have to go out.

"After awhile, living alone like that, I found myself pretending that I had a medical condition that couldn't be treated. That way I didn't have to hate myself for being afraid to do anything about it."

Miss Gillon was forced to rethink her position when the tick got so heavy she couldn't stand it any longer. Reluctantly, she made an appointment with Dr. Franck, who removed the 14.3-pound tick by separating the body from the head with a scalpel.

"I also performed minor surgery to removed the tick's head from her flesh," said the doctor. "She was so grateful that she broke down and cried. It was the end of a terrible burden."

Although Miss Gillon's tick was a whopper it wasn't a world record. Veterinarians removed a 16-pound tick from an elephant in Kenya in 1967.